Disorders of Volume: Core Curriculum 2025

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Historically, the paradigm for all maladies was associated with an imbalance of the 4 humors: blood, black bile, yellow bile, and phlegm. Although our understanding of disease has evolved significantly since the time of Hippocrates, a similar cornerstone of inpatient and ambulatory care involves understanding and correcting imbalances of volume. The kidneys are the principal organs controlling extracellular volume, capable of both sensing and altering salt retention through multiple redundant pathways, including the sympathetic nervous system and the renin-angiotensin-aldosterone system. Various disease states including sepsis, heart failure, and liver cirrhosis can dramatically alter the movement of volume across body compartments, leading to pathologic responses. Greater understanding of the role of the endothelial glycocalyx, the harms of volume overload among critically ill patients, and the impact of venous congestion on kidney function has challenged the traditional paradigms of volume management. Because both hypovolemia and hypervolemia are symptomatic conditions associated with adverse outcomes, managing volume is an essential skill for the nephrologist. In this Core Curriculum, we review the physiology of volume disorders and management strategies through a series of clinical cases.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Approximately 60% of body weight is fluid, commonly referred to as total body water, which is primarily composed of water containing sodium, potassium, and chloride. The remaining 40% is solid tissue, primarily bone. Two-thirds of our total body water is located in the intracellular space and one-third in the extracellular space. The extracellular space is further divided into the interstitial space, containing three-fourths of the extracellular volume, and plasma or intravascular space, containing the remaining one-fourth of extracellular volume (Fig 1).

In this installment of *AJKD*'s Core Curriculum in Nephrology, we discuss disorders of volume, which are typically identified clinically as changes in the extracellular space, and management strategies through a series of clinical vignettes. At the extremes, hypovolemia can impair tissue perfusion leading to shock, and hypervolemia can cause acute hypoxemic respiratory failure. Recently, even moderate hypervolemia has been associated with adverse outcomes and increased mortality.

Case 1: *A 54-year-old woman with type 2 diabetes was admitted to the medical intensive care unit for septic shock due to ascending cholangitis. She received 3 liters of intravenous fluids and was treated with piperacillin/tazobactam and norepinephrine. An endoscopic retrograde cholangiopancreatography was performed successfully with choledocholithiasis retrieval on hospital day 3. Her blood pressure improved to 98/55 by day 4, and norepinephrine was discontinued. On her current examination, she has pitting edema of her upper and lower extremities. She has no jugular venous distention, her lungs are clear, and she has 3-second capillary refill. Her urine output has been at least 0.5 mL/kg per hour.*

Question 1: What is the mechanism of the most likely cause of extracellular volume excess in this patient?

(a) Decreased cardiac inotropy
(b) Increased antidiuretic hormone secretion
(c) Increased capillary permeability
(d) Decreased oncotic pressure

For the answer to this question, see the following text.

This patient has edema, which indicates extracellular volume excess and specifically expansion of the interstitial compartment. The osmolarity of the intracellular and extracellular compartments is identical under physiologic conditions. However, the intracellular compartment has a potassium concentration of about 140 mEq/L and a sodium concentration of about 10 mEq/L, whereas the extracellular compartment has a potassium concentration of about 4 mEq/L and a sodium concentration of about 140 mEq/L. This difference is maintained by the actions of the adenosine triphosphate sodium-potassium pump. Most cell membranes are permeable to water but require transporters to move sodium,

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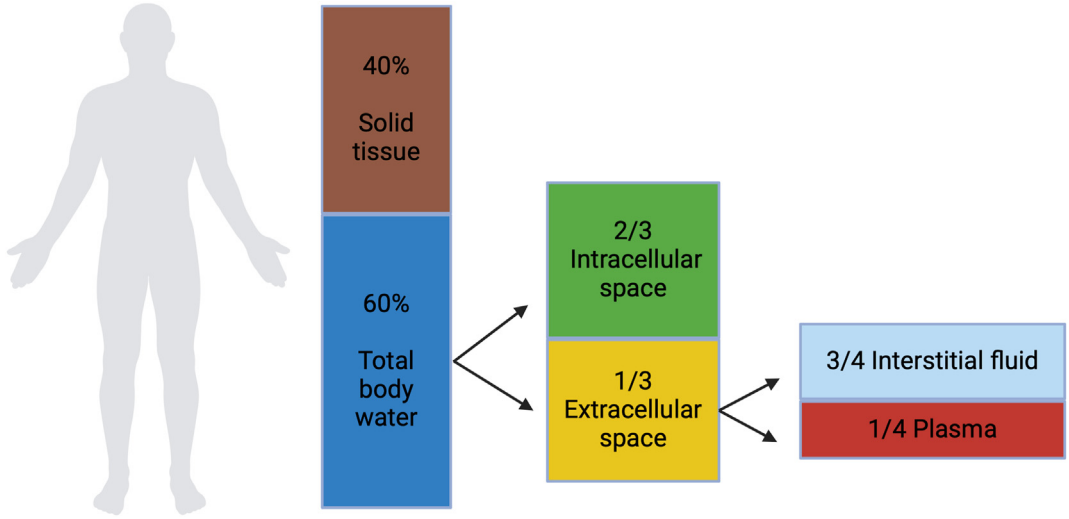

Figure 1. Body fluid compartments.

potassium, and chloride. Therefore, when water is added to the intravascular compartment, it quickly equilibrates into all 3 compartments. Because the intracellular compartment is twice as large as the extracellular compartment, the primary effect is cell enlargement. When isotonic fluid is added to the intravascular compartment, it exclusively equilibrates within the extracellular compartment.

Movement within the extracellular compartment is determined largely by plasma hydrostatic pressure and capillary permeability. Traditional Starling's forces suggest that high hydrostatic pressures favor fluid movement across a semipermeable membrane and high oncotic pressures oppose fluid movement. This proposed phenomenon was a 2-way street in which fluid could move back into the intravascular space from the interstitial space. Fluid was thought to be filtered to the interstitium at the arteriolar end of the capillaries where hydrostatic pressure was high and absorbed back at the venular end where oncotic pressure was higher. However, there is no pressure gradient that drives fluid back into the intravascular compartment. Therefore, the model is empirically a 1-way street. Interstitial fluid is removed predominantly by lymphatic drainage.

Capillary permeability is another major determinant of transcapillary fluid movement particularly in pathologic states. The endothelial glycocalyx is a layer of proteoglycans, glycosaminoglycan side chains, and sialoproteins. Albumin, thrombomodulin, and cell adhesion molecules among other serum proteins are bound to the luminal portion of the glycocalyx. The glycocalyx is relatively impermeable to albumin in healthy states due to the negative charge of glycosaminoglycans side chains. However, in states of inflammation, ischemia, and sepsis, the glycocalyx breaks down. There is increased filtration of proteins into the interstitium through endothelial clefts, which contributes to the hypoalbuminemia seen in critically ill patients (Fig 2). The transcapillary rate of albumin escape may be as high as 20% in these conditions as opposed to 5% under physiologic conditions.

The correct answer is therefore choice (c), increased capillary permeability. Hypoalbuminemia and consequent decreased oncotic pressure are effects of critical illness, but not the cause of edema in this patient. Decreased cardiac inotropy may occur due to septic cardiomyopathy, but this is unlikely given the lack of jugular vein distention on examination and improvement in blood pressures. Antidiuretic hormone (ADH) secretion from the posterior pituitary gland is increased in sepsis due to low pressures sensed in the peripheral baroreceptors and through the effects of angiotensin II. In sepsis, the sympathetic nervous system up-regulates the renin-angiotensin-aldosterone system via adrenergic receptors in the granular cells. Angiotensin II can then directly increase ADH secretion. However, ADH increases the reabsorption of water (not salt) in the kidney, and water will equilibrate through all fluid compartments, with one-third remaining in the extracellular space. Therefore, this is not the best answer choice.

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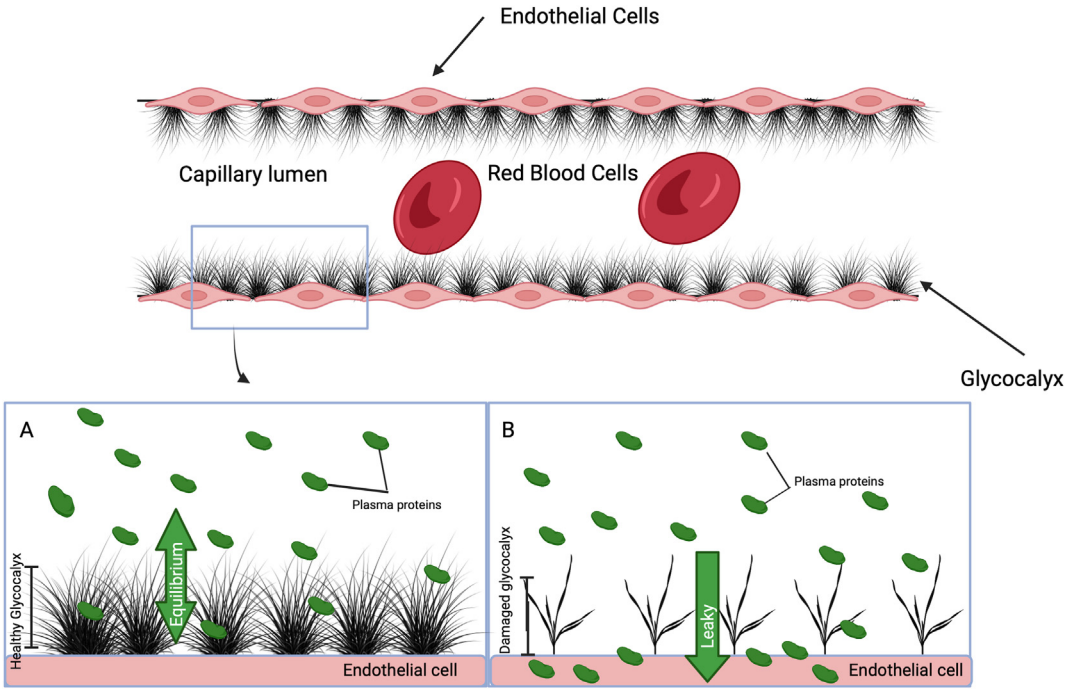

Figure 2. Capillary permeability with an (A) intact glycocalyx and a (B) damaged glycocalyx, which occurs in states of inflammation, sepsis, and ischemia.

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Case 2: *A 60-year-old woman with heart failure with reduced ejection fraction is admitted to the hospital with shortness of breath with minimal exertion, orthopnea, increased lower extremity edema, and weight gain. She recently returned from a road trip where her diet consisted primarily of meals purchased at fast food restaurants. She denies any recent medication changes, fever, chills, or chest pain. Her home medications include furosemide, 40 mg daily; metoprolol succinate, 50 mg daily; valsartan, 160 mg daily; spironolactone, 25 mg daily; and aspirin, 81 mg daily. Her blood pressure is 150/78 mm Hg; pulse is 86 bpm; respiratory rate is 22 breaths/min; and she has an oxygen saturation of 97% with 2 L of supplemental oxygen. On examination she is tachypneic with pulmonary rales. Jugular venous pressure is at the angle of her mandible, and she has 2+ pitting edema in her lower extremities. She is warm to the touch. Her laboratory results are as follows:*

Laboratory Results	Today	Reference Range
Na, mEq/L	135	140
K, mEq/L	4.9	4.0
Cl, mEq/L	105	110
CO_2, mEq/L	23	24
SUN, mg/dL	63	24
Creatinine, mg/dL	2.2	1.2

Question 2: What Is The Next Best Step In Management?

(a) Discontinue valsartan.
(b) Initiate ultrafiltration.
(c) Prescribe furosemide intravenously.
(d) Initiate dobutamine.

For the answer to this question, see the following text.

Historically, acute kidney injury (AKI) in patients with heart failure has been simplified to a model of reduced cardiac output from a failing left ventricle resulting in decreased renal blood flow. Although it is intuitive, this model requires severely depressed cardiac output as glomerular filtration rate is maintained, primarily via vasoconstriction of the efferent arteriole, until renal blood flow declines beyond the autoregulatory threshold of the kidney. Recently, the role of venous congestion has garnered increased attention due to its consistent association with worsening kidney function. This has led to efforts at decongestion emerging as a central tenet in the management of hospitalized patients with acute decompensated heart failure. Whether this relationship is causal is not yet clear, but there is increasing likelihood that venous congestion plays a vital role in a complex interplay of factors, including macro and microcirculatory dysfunction, leading to AKI (Fig 3).

The impact of venous congestion on kidney function has been known for decades, with experimental models demonstrating significant reductions in renal blood flow and urine output with elevations in renal venous pressure (RVP) while maintaining constant arterial pressure. Animal models have demonstrated transmission of elevated central venous pressure to renal veins, which has several adverse effects. A rise in RVP results in a lower arteriovenous

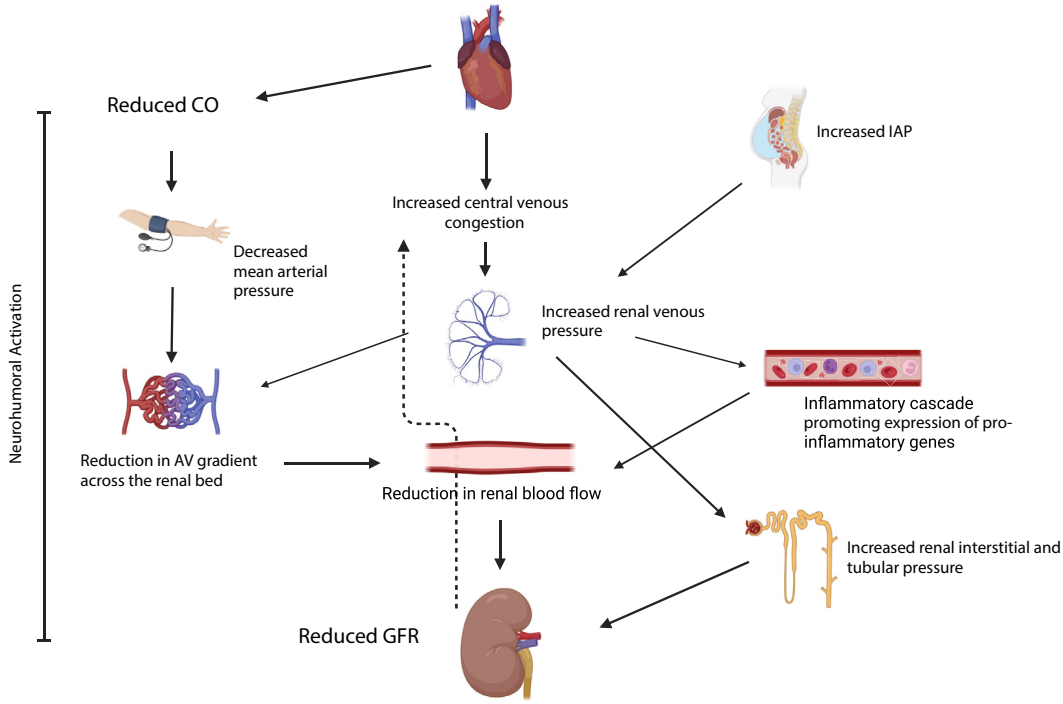
Reduced CO
Increased IAP
Increased central venous congestion
Decreased mean arterial pressure
Increased renal venous pressure
Neurohumoral Activation
Inflammatory cascade promoting expression of pro-inflammatory genes
Reduction in AV gradient across the renal bed
Reduction in renal blood flow
Increased renal interstitial and tubular pressure
Reduced GFR

Figure 3. Association of venous congestion and impairment in glomerular filtration rate. Abbreviations: AV, arteriovenous; CO, cardiac output; IAP, intra-abdominal pressure; GFR, glomerular filtration rate.

gradient across the renal bed, decreasing renal perfusion pressure and impairing renal blood flow. The juxtaglomerular apparatus is composed of 4 components: the terminal portion of the afferent glomerular arteriole, the macula densa, the extraglomerular mesangial region, and the efferent arteriole, which is sensitive to changes in renal perfusion pressure. This causes it to function independently from systemic baroreceptors and results in the stimulation of renin release, which increases linearly with RVP and precedes changes in renal blood flow and glomerular filtration rate (GFR).

Sympathetic stimulation, which is up-regulated in patients with heart failure, causes vasoconstriction, reducing splanchnic capacitance, which normally plays an essential role in maintaining optimal cardiac preload. Splanchnic congestion, even in the absence of frank ascites, results in elevations in intra-abdominal pressure and is independently associated with impaired kidney function at pressures > 8 mm Hg. Reductions in intra-abdominal pressure have demonstrated restoration of normal kidney function.

Animal models have shown an increase in renal interstitial pressure (RIP) that rises proportionally with an increase in RVP. The rise in RIP is initially offset by a compensatory increase in lymphatic flow. However, a progressive rise in RIP against a rigid renal capsule, which is resistant to expansion, may create a tamponade like effect, leading to tubular compression. This increase in tubular pressure opposes filtration, resulting in a decrease in glomerular filtration rate (GFR). This is supported by experimental models demonstrating amelioration of kidney injury with decapsulation.

In murine models, elevations in RVP are associated with changes in renal hemodynamics, including vasoconstriction, a reduction in renal blood flow, and an increase in renal vascular resistance. Interestingly, these changes were not observed in denervated kidneys, suggesting a compulsory role of the sympathetic nervous system, which is initially beneficial as a compensatory response but becomes maladaptive with further preglomerular vasoconstriction, as well as proximal tubular sodium reabsorption, worsening AKI, and volume overload.

Finally, venous congestion has been shown to trigger an inflammatory cascade through activation of nuclear factor κ B, which promotes expression of proinflammatory genes that have a downstream effect of transitioning endothelial cells to a proinflammatory and vasoconstricting state by interfering with endothelial maintenance of central venous tone via nitric oxide, which further impairs renal blood flow.

The patient in this case is admitted with acute decompensated heart failure and signs of volume overload despite outpatient diuretics. The next best step in therapy is to initiate intravenous loop diuretics at 2.5 times the patient's home dose; therefore, choice (c) is correct. Discontinuation of valsartan may be necessary if she develops hypotension or hyperkalemia, but currently this is not needed. Ultrafiltration is an effective therapy for volume removal; however, it has been associated with increased adverse events compared to diuretic therapy. There is no indication

that the patient is in a low flow state, and initiation of an inotrope, such as dobutamine, is not indicated.

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The Role of Chloride

Case 3: *A 65-year-old man with stage G4A2 chronic kidney disease (CKD), type 2 diabetes, and hypertension is seen for routine follow-up evaluation. He has had progression of his CKD over the past 2 years. His laboratory tests are notable for serum creatinine, 3.1 mg/dL; estimated GFR, 18 mL/min/1.73 m²; serum potassium, 4.5 mEq/L; and serum bicarbonate, 15 mEq/L. His blood pressure is 128/74 mm Hg on therapy with losartan, amlodipine, and chlorthalidone. You decide to initiate alkali therapy with sodium bicarbonate tablets.*

Question 3: What is the most likely side effect of this therapy?

(a) Worsening hypertension
(b) Heart failure
(c) Nausea
(d) Lower extremity edema

For the answer to this question, see the following text.

Several trials of sodium bicarbonate administration to patients with metabolic acidosis across a wide spectrum of CKD stages have failed to demonstrate increased rates of hypertension, lower extremity edema, or new onset heart failure, so choices (a), (b), and (d) are incorrect. In this case, the most common adverse effect of the options provided that is associated with oral sodium bicarbonate therapy is nausea, so choice (c) is correct.

The lack of observed volume overload may be a result of sodium loading without chloride. Despite being the first electrolyte to be easily measured in blood, chloride, the most abundant anion in the body, has been historically denigrated for serving little purpose other than maintaining electroneutrality as a counterpart of sodium. The discovery of pendrin and the role chloride plays in ameliorating metabolic alkalosis independent of sodium administration, termed "chloride-responsive" alkalosis, as well as increasing interest in its role in heart failure pathophysiology, have provided a bit of a renaissance for chloride in recent years. Volume homeostasis and disorders of sodium are undoubtedly linked; however, although the terms sodium and salt are often conflated, chloride plays a substantial role. Early physiologic studies demonstrated similar increases in sodium retention, weight gain, and suppression of plasma renin activity and plasma aldosterone with administration of sodium chloride versus equimolar amounts of nonhalide sodium salts, such as sodium bicarbonate, sodium phosphate, and sodium citrate. However, only sodium chloride administration resulted in elevations in blood pressure and increases in plasma volume.

The change in plasma volume observed only with a combination of sodium and chloride administration suggests a significant impact of chloride on the distribution of fluid between the vascular and extravascular compartments. It seems that sodium loading, in the absence of chloride, sequesters sodium in tissue sites, where it is rendered osmotically inactive. Similarly, selective chloride loading, in the absence of sodium, fails to produce hypertension in rats, suggesting a symbiotic relationship between sodium and chloride in producing hypertension. Clinically this was demonstrated in a large cluster-randomized trial showing a reduction in major adverse cardiovascular events when a proportion of dietary sodium chloride was substituted with potassium chloride. It should be emphasized that these data are primarily relevant to oral sodium administration in ambulatory patients. Intravenous sodium solutions, irrespective of anion (ie, isotonic sodium bicarbonate), have the potential to increase extracellular volume, likely due to the rapidity of administration.

A particular area of interest is the role of chloride in patients with heart failure. Hypochloremia has been associated with a worse prognosis, an effect that is independent of serum sodium levels. Chloride is the principal regulator of renin release from the macula densa in the juxtaglomerular apparatus, and hypochloremia has been associated with diuretic resistance via interaction with with-no-lysine (WNK) kinases that regulate sodium reabsorption through the sodium/potassium/chloride cotransporter 2 (NKCC2) and the sodium/chloride cotransporter (NCC), worsening neurohumoral activation and volume overload, respectively. A proposed hypothesis has suggested chloride is the primary regulator of changes in plasma volume in patients with heart failure, but this theory has not yet gained widespread acceptance, and the possible therapeutic implications remain unclear.

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Case 4: *A 68-year-old man with CKD stage 3a, hypertension, and depression presents to the emergency department due to worsening fatigue. He has been eating 1 small meal a day for the last 2 weeks due to depression from a recent divorce. He had 1 episode of dark stool 2 days ago and more frequent stools of 2-3 per day. He had a fall while walking from the parking lot to the emergency department due to lightheadedness. His medications include empagliflozin, 10 mg daily; fluoxetine, 20 mg daily; and losartan, 50 mg daily. He has been taking ibuprofen as needed for shoulder pain. He has a decrease in blood pressure from 107/65 to 85/54 when standing from a seated position. He is given 2 liters of 0.9% saline, and laboratory tests are ordered.*

Laboratory Results	Today	5 mo Ago
Na, mEq/L	135	140
K, mEq/L	5.6	4.2
Cl, mEq/L	105	99
CO_2, mEq/L	15	22
SUN, mg/dL	97	28
Creatinine, mg/dL	3.9	1.5
Glucose, mg/dL	88	105
Hemoglobin, g/dL	10.5	13.1

Question 4: What product should be administered at this time?

(a) One unit of packed red blood cells
(b) 500 mL of 5% albumin
(c) 1 L of 0.9% saline
(d) 1 L of isotonic sodium bicarbonate

For the answer to this question, see the following text.

This patient has symptoms and signs of volume depletion. His history of poor oral intake, frequent stools, and use of empagliflozin, a sodium/glucose transport inhibitor, indicates both urinary and gastrointestinal (GI) volume losses without adequate repletion. Additionally, his use of the nonsteroidal anti-inflammatory medication ibuprofen prevents the normal prostaglandin-mediated afferent arteriole vasodilation in response to renin secretion. Therefore, the vasoconstrictive effects of angiotensin II remain unopposed, and renal blood flow further decreases. His low GFR decreases regeneration of bicarbonate in the cortical collecting duct, resulting in a persistent metabolic acidosis likely generated by lower GI bicarbonate loss.

Daily losses of hypotonic fluid occur through sweat, stool, and urine. Skin losses tend to be about 500 mL per day. In the setting of excessive perspiration due to hyperthermia or physical exertion, the volume losses can be as high as 3 L/hour. Sodium concentration in sweat varies from 5 mEq/L to 90 mEq/L. Eccrine glands initially secrete fluid that is isotonic to plasma but then, modified by reabsorption of the sodium and chloride along the duct, ultimately secrete hypotonic fluid at the skin surface. People with cystic fibrosis are unable to reabsorb sodium and chloride due to variants of the CFTR chloride channel and secrete sodium concentrations greater than 60 mEq/L at rest. People who are carriers of this variant have higher sweat sodium concentration and are at higher risk for volume depletion and metabolic alkalosis.

GI fluid changes in composition along the GI tract due to distinct groups of ion transporters and channels. About 8 L of fluid are secreted each day, and most are reabsorbed in the small intestine and colon. The sodium concentration of stool is 20-30 mEq/L but can rise to 100 mEq/L in inflammatory or secretory diarrhea. Ileostomy drainage has a higher sodium concentration of 40-90 mEq/L and lower potassium concentration, raising the risk of volume depletion with hyperkalemia.

The kidney can excrete urine that is virtually sodium free to maintain intravascular volume. Obligate urine losses are 500 mL per day to excrete daily waste in people who can maximally concentrate their urine. Urinary volume losses may occur due to pharmacologic therapy with diuretics or tubular disorders that mimic diuretics such as Bartter syndrome or Gitelman syndrome. Estimated sodium losses from both renal and extrarenal sites are displayed in Table 1.

Osmotic aquaresis occurs when glucose, mannitol, or urea limit isosmotic water reabsorption in the proximal tubule. This may occur with hyperglycemia, administration of mannitol for cerebral edema, and recovery in AKI in which there are large amounts of filtered urea. Because these states result in *water* excretion, relatively large losses are required to affect volume status. Though sodium/glucose transport inhibitors increase glucosuria, the natriuresis from blocking sodium reabsorption is the principal cause of volume losses. Ventilation also results in water losses through water vapor. However, ventilatory water losses are generally balanced by carbohydrate metabolism to CO_2 and H_2O because both processes occur in a 1:1 proportion. Additionally, water loss primarily affects the intracellular compartment and has a small effect on extracellular volume.

This volume-depleted patient has a normal anion gap acidosis, AKI, and an elevated potassium concentration. Therefore, fluid containing bicarbonate would be an appropriate choice of volume repletion, so choice (d) is correct. His increased stool volume suggests that he has incurred bicarbonate losses, and his baseline CKD with superimposed AKI will result in delayed regeneration of bicarbonate by the kidney. Furthermore, bicarbonate administration will lower his potassium concentration whereas 0.9% saline (choice c) may raise it by worsening his metabolic acidosis.

Table 1. Estimated Renal and Extrarenal Sodium Losses

	[Na^+] mmol/L	Volume Range (L/d)
Sweat	5-90	0.5
Exercise	5-90	0.2-8
Cystic fibrosis	60-150	0.5
Stool	20-30	<0.15
Inflammatory diarrhea	20-100	1-3
Ileostomy	40-90	0.5-1
Vomitus	20-100	0-3
Loop diuretic	50-150	2-6

It is possible that he has an elevated serum potassium concentration due to cellular shifts but low total body potassium stores. However, because potassium removal is much more resource intensive than repletion, it would be best to err on the side of caution. In the BICAR-ICU trial of fluid resuscitation in critically ill patients with metabolic acidosis, a bicarbonate infusion to a target pH of 7.3 resulted in less need for renal replacement therapy for hyperkalemia. Notably, this trial included patients with lactic acidosis and excluded patients with GI bicarbonate losses. The clinician should check ionized calcium concentration during bicarbonate infusion. This value will decrease with bicarbonate administration as the rising pH decreases hydrogen ion binding to albumin, allowing more calcium to bind albumin.

Though studies of oral sodium bicarbonate repletion in people with CKD have raised doubt as to whether sodium bicarbonate increases extracellular volume to the same degree as sodium chloride, these results cannot be extrapolated to intravenous administration. Studies have consistently shown that sodium bicarbonate increases cardiac output and mean arterial pressure to the same degree as 0.9% saline.

The administration of colloid (choice b) has not been shown to be superior to crystalloid for resuscitation in multiple patient populations, excluding those with cirrhosis. These trials were performed based on the theory that the greater oncotic pressure of colloid would allow this fluid to remain in the intravascular space. Because the intravascular compartment is 25% of the extracellular volume, one-fourth the volume of colloid would be expected to have the same resuscitative effect of 1 liter of crystalloid. However, in the Saline Versus Albumin Fluid Evaluation (SAFE) trial, albumin administration volumes were 70% those of saline to achieve similar resuscitation targets. Therefore, fluid balance is not significantly impacted by using albumin over crystalloid. Though this patient may be having an upper GI bleed, lower hemoglobin thresholds for transfusion of 7 g/dL have shown to improve survival compared with higher thresholds. Therefore, choice (a) is incorrect.

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Case 5: *A 73-year-old man with diabetes, body mass index of 38, and obstructive sleep apnea is seen in the clinic with worsening abdominal distension over the last month. On examination, he has clear lungs, no visible jugular venous distension, and no edema. His heart is in a regular rhythm, and no murmurs are heard. His abdomen is soft but distended with shifting dullness and venous collaterals seen above the umbilicus. He has no abdominal tenderness. Laboratory tests performed before his visit show normal kidney and liver function. He denies fevers, weight loss, or abdominal pain.*

Question 5: What is the most likely finding on further workup?

(a) Pulmonary hypertension
(b) Splenomegaly
(c) Acquired thrombotic disorder
(d) Malignancy

For the answer to this question, see the following text.

Clinical ascites is the consequence of an accumulation of fluid within the peritoneal cavity, which may result from increased hydrostatic pressure and increased capillary permeability. The most common cause of ascites in the United States is portal hypertension due to cirrhosis. Other causes of portal hypertension include acute hepatitis or acute liver failure, hepatic vein outflow obstruction (Budd-Chiari syndrome), left- or right-sided heart failure, or constrictive pericarditis. Increased permeability of the peritoneal membrane may be due to infection or malignancy. Rarely, severe hypoalbuminemia may be the only identified cause of ascites.

This patient's body mass index of 38 and diabetes are risk factors for metabolic associated fatty liver disease (MAFLD), and his abdominal venous collaterals indicate portal hypertension. MAFLD is rising globally and is the second leading cause of cirrhosis in the United States. As liver fibrosis progresses to cirrhosis, there is increased hepatic resistance to portal flow, shunting of blood to the systemic circulation via collateral veins, and increased production of circulating vasodilators, primarily nitric oxide. These factors result in splanchnic arterial vasodilation which increases portal vein inflow, thereby worsening portal hypertension. Effective arterial blood volume is maintained due to an increase in cardiac output. Eventually the decrease in systemic vascular resistance activates the sympathetic nervous system and the renin-angiotensin-aldosterone system, resulting in volume retention (Fig 4). Portal hypertension is strongly associated with splenomegaly due, in part, to congestion of the red pulp and other hyperproliferative mechanisms. Therefore, choice (b) is correct.

Though this patient has obstructive sleep apnea, a risk factor for pulmonary hypertension and right-sided heart dysfunction, his lack of jugular vein distention makes a cardiac cause unlikely (choice a). An acquired thrombotic disorder could cause a hepatic vein thrombosis or portal vein thrombosis. Hepatic vein thrombosis is a rare cause of hepatic vein outlet obstruction, also known as Budd-Chiari syndrome, and is strongly associated with myeloproliferative diseases. Ascites is seen when the hepatic outlet obstruction develops acutely but may be absent in subacute cases due to portal and hepatic vein collaterals. Though the clinical presentation ranges from asymptomatic to acute liver failure, transaminases are often elevated. Portal vein thrombosis without cirrhosis does not typically result in ascites because the obstruction is presinusoidal, and sinusoidal hypertension is generally required for ascites formation, so choice (c) is incorrect. Malignancy (choice d) may involve the peritoneum leading to increased peritoneal capillary permeability; however, this should not result in features of portal hypertension such as prominent venous collaterals of the abdomen.

The combination of a loop diuretic and a mineralocorticoid receptor antagonist have been used conventionally to treat ascites. This practice was popularized in the 1980s due to 2 small, randomized trials of furosemide versus spironolactone in people with cirrhosis. One study showed that single-agent furosemide was effective but required escalating doses and significant potassium repletion. The other study demonstrated a better response rate to spironolactone as a single agent or in combination with furosemide than furosemide alone. One hypothesis for this finding is that hepatic dysfunction alters the abundance of organic anion transporter 1 (OAT1) on the basolateral side of the proximal tubular epithelial cell, preventing adequate secretion of furosemide by OAT1 to its tubular site of action. Animal studies have shown that extrahepatic cholestasis causes up-regulation of OAT1 and increased furosemide secretion in the short-term but down-regulation long-term. However, this hypothesis requires confirmation. More contemporary studies have shown that the use of single-agent spironolactone results

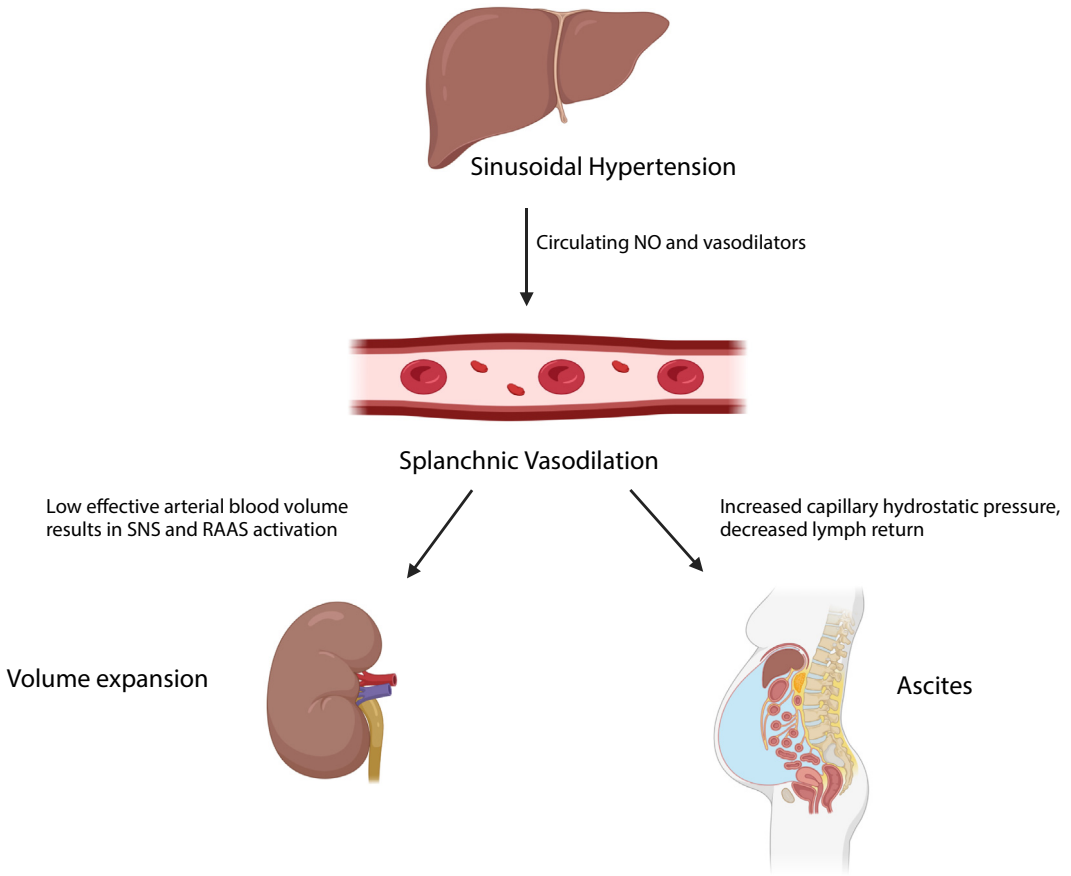
Sinusoidal Hypertension
Circulating NO and vasodilators
Splanchnic Vasodilation
Low effective arterial blood volume results in SNS and RAAS activation
Increased capillary hydrostatic pressure, decreased lymph return
Volume expansion
Ascites

Figure 4. Physiology of ascites formation. Abbreviations: NO, nitric oxide; RAAS: renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

in higher rates of hyperkalemia, and therefore lower doses should be used in people with kidney disease. In contrast, hypokalemia may contribute to the development of hepatic encephalopathy, and furosemide should be used judiciously in people with inadequate nutrition.

Additional Readings

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